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(54) Optically active alcohols and processes for the preparation thereof

(57) The present invention relates to an optically active alcohol and the analogue thereof, i.e., (+)-cis-4-cumyloxy-2-cyclopenten-1-ol (1) and (-)-cis-1-acyloxy-4-cumyloxy-2-cyclopentene (2), which are useful as intermediates for biologically active compounds such as prostaglandins, and processes for preparing them. The invention also relates to the use of the optically active alcohol and the analogue thereof for the preparation of (-)-oxabicyclo[3.3.0]oct-6-en-3-one.

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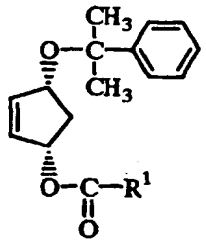
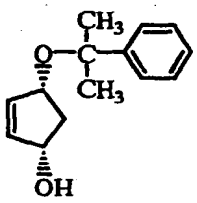


(2)

wherein R^1 is a hydrogen atom or a straight or branched C_1-C_{10} alkyl group, optionally any hydrogen atom in the alkyl group being substituted by a halogen atom.

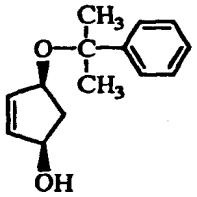
[0010] Examples of the alkyl group for R^1 in formula (2) include, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, chloromethyl, dichloromethyl and trichloromethyl. Preferably, R^1 is methyl. Thus, a preferable compound of formula (2) is (-)-cis-1-acetoxy-4-cumyloxy-2-cyclopentene.

[0011] The present invention also provides an optically active compound, i.e., (-)-cis-4-cumyloxy-2-cyclopenten-1-ol, represented by formula (3)



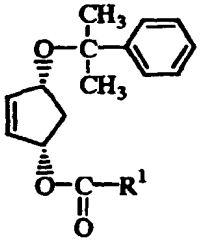
(3)

[0012] The present invention also provides a process for preparing optically active compounds of formula (1)



(1)

and formula (2)

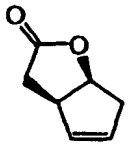


(2)

wherein R^1 is a hydrogen atom or a straight or branched C_1-C_{10} alkyl group, optionally any hydrogen atom in the alkyl group being substituted by a halogen atom, which comprises treating (±)-cis-4-cumyloxy-2-cyclopenten-1-ol of formula (4)

(a2) treating the compound (a-1) with an acid in a solvent to form the compound of formula (6).

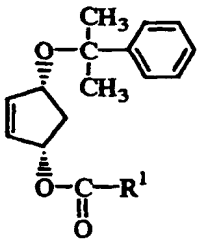
[0015] The invention also provides a process for preparing an (-)-oxabicylco[3.3.0]oct-6-en-3-one of formula (6)



(6)

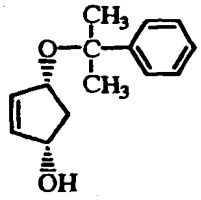
which comprises steps of;

(b1) subjecting a compound of formula (2)



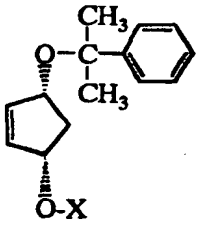
(2)

wherein R^1 is as defined above to alcoholysis to form a compound of formula (3)



(3)

(b2) protecting a hydroxyl group of the compound (3) by a suitable protecting group to form a compound of formula (b-2)

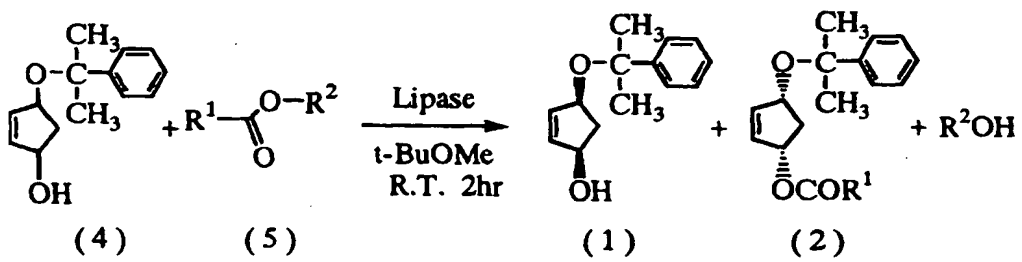


(b-2)

wherein X is a protecting group,
(b3) treating the compound (b-2) with an alkaline metal in ammonia to form a compound of formula (b-3)

(+)-cis-4-cumyloxy-2-cyclopenten-1-ol and (-)-cis-1-acyloxy-4-cumyloxy-2-cyclopentene, are shown in the following scheme A.

[Scheme A]



(4) (5) (1) (2)

[0024] The optically active compounds of formulas (1) and (2) can be prepared by subjecting the racemic compound (4) to the transesterification by treating with immobilized lipase (Lipase PS originated from *pseudomonas* sp., manufactured by Amano Pharm. Co., Ltd.) and carboxylic acid ester (5) in t-butyl methyl ether and then isolating the products by silica gel column chromatography.

2. Preparation of (-)-oxabicylco[3.3.0]oct-6-en-3-one

[0025] A process for preparing the title compound in which (+)-cis-4-cumyloxy-2-cyclopenten-1-ol is used as a starting material is illustrated below, in order of steps (a1) to (a2).

Step (a1)

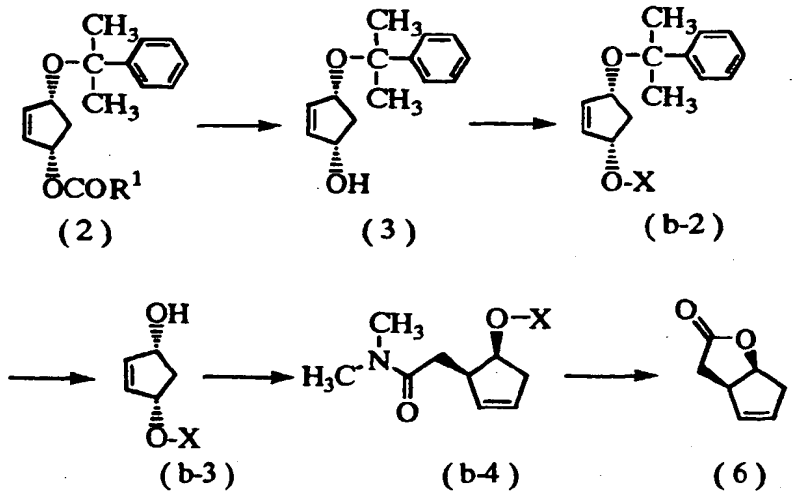
[0026] The alcohol of formula (1) is heated with dimethylacetamide dimethyl acetal in a refluxing organic solvent to afford 3R,4S-N,N-dimethyl-4-cumyloxycyclopentenyl-3-acetamide. Examples of solvents which can be used in the step include hydrocarbon solvents such as hexane, heptane, cyclohexane and toluene; alcohols such as methanol, ethanol and propanol; ketones such as acetone and methylethyl ketone; ethers such as diethyl ether, dimethyl ether, diisopropyl ether, diphenyl ether, methyl buthyl ether, tetrahydrofuran and dioxane; and non-protonic polar solvents such as dimethylformamide, dimethylacetamide and dimethylsulfoxide. Preferably, the solvent is diphenyl ether. The reaction temperature is in the range of 200°C to 300°C, preferably 250°C to 280°C, e.g. 280°C. The reaction time varies dependent on the temperature. For example, at the reaction temperature of 280°C, the reaction time is preferably within 30 minutes.

Step (a2)

[0027] The compound from the step (a1) is treated with an acid in the solvent to afford the intended compound. The reaction temperature is in the range of 0°C to 30°C, e.g. room temperature. The reaction time varies dependent on the temperature. At room temperature, for example, the reaction time is in the range of 1 to 24 hours, preferably 12 hours. The solvents which can be used in this step are solvents examplified for the step (1). Preferably, the solvent is dioxane. Examples of the acid which may be used in this step are, but not limited to, a diluted inorganic or organic acid, e.g. hydrochloric acid, sulfuric acid, p-toluenesulphonic acid and pyridinium p-tolunesulfonate. Preferably, the acid is diluted hydrochloric acid or diluted sulfuric acid, e.g. 10% hydrochloric acid. Accordingly, the step is preferably carried out in a mixture of 10% hydrochloric acid and dioxane at the ratio 1:1.

[0028] The steps as mentioned above are shown in the following scheme B.

[Scheme C]



[0037] In a preferable embodiment of the present invention, the compound (2) is subjected to the hydrolysis of the ester group by treating with alkaline in methanol, i.e. the Eschenmoser reaction to afford the mono-hydroxyl compound (3), (-)-cis-4-cumyloxy-2-cyclopenten-1-ol (step b1). The hydroxyl group is protected with t-butyldimethylsilyl group (step b2) and then the compound (b-2) is treated with sodium/ammonia to give the mono-hydroxyl compound of formula (b-3) (step b3). The resulting compound (b-3) is processed in the same manner as step (a1) to afford the amide (b-4) (step b4). The amide (b-4) is subjected to the hydrolysis and the intramolecular cyclization by treating with a diluted hydrochloric acid to afford the compound (6) (step b5).

[0038] The invention is further illustrated by the following Examples. These examples are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1

Preparation of (+)-cis-4-cumyloxy-2-cyclopenten-1-ol and (-)-cis-1-acetoxy-4-cumyloxy-2-cyclopentene

[0039] A solution of (±)-cis-4-cumyloxy-2-cyclopenten-1-ol (1.071g, 4.91 mmol) and 2.5 ml of vinyl acetate was stirred with Lipase PS immobilized on Celite (1.0 g) at room temperature for 2 hours. After the reaction, the reaction mixture was subjected to filtration to remove the enzyme and then the solvent was distilled off under reduced pressure. The residue was purified on silica gel column (n-hexane/ ethyl acetate = 1/4 to 1/2) to afford (+)-cis-4-cumyloxy-2-cyclopenten-1-ol (535 mg, 50% yield), with the following data:

$[\alpha]_D^{31}$ +27.52° (c 1.11, $CHCl_3$)
IR ν max (neat) cm^{-1}: 3410
^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.56 (3H, s), 1.58 (3H, s), 1.61 (1H, ddd, *J* = 13.8, 7.2, 7.2 Hz), 2.57 (1H, ddd, *J* = 13.8, 4.8, 4.8 Hz), 4.05-4.12 (1H, m), 4.43-4.52 (1H, m), 5.83 (1H, ddd, *J* = 5.7, 1.5, 1.5 Hz), 5.91 (1H, ddd, *J* = 5.7, 1.5, 1.5 Hz), 7.23-7.48 (5H, m)
^{13}C-NMR (75MHz, $CDCl_3$) δ: 28.64, 29.60, 43.94, 74.98, 76.20, 77.84, 126.18, 127.17, 128.32, 136.07, 136.17, 146.82
MS m/z: 203 (M + -Me)
Exact mass calcd. for $C_{13}H_{15}O_2$ (M + -Me): 203.1072 Found: 203.1054
Anal. calcd. for $C_{14}H_{18}O_2$ (M +): C, 77.03, H, 8.31. Found: C, 76.59, H, 8.04;

and

under the standard condition (t-butyldimethylsilyl chloride and imidazole in DMF, at 0°C for 180 minutes) to afford (-)-cis-1-(t-butyldimethyl silyloxy)-4-cumyloxy-2-cyclopentene in 97% yield. The compound obtained was then treated with sodium in ammonia and tetrahydrofuran (THF) to afford the mono-hydroxyl compound, $[\alpha]_D^{30}$ -24.53(1.59, CH_2Cl_2) (b-3), in 83% yield. The mono-hydroxyl compound was refluxed with dimethylacetamide dimethyl acetal in diphenyl ether (20 ml) at 280°C for a period of 30 minutes under the same condition as Example 2 to afford 3R,4S-N,N-dimethyl-4-(t-butyldimethyl silyloxy)-cyclopentenyl-3-acetamide (b-4), $[\alpha]^{27}_D$ -56.55(c 1.01, $CHCl_3$), in 77% yield. The compound (b-4) was then stirred in a mixture of 10% hydrochloric acid and dioxane (1:1) at room temperature for a period of 12 hours to afford (-)-oxabicylco[3.3.0]oct-6-en-3-one in 87% yield, with the following data:

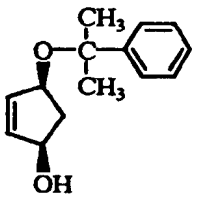
mp 43-44°C
$[\alpha]_D^{29}$-103.21° (c 1.02, MeOH)
IR ν max (neat) cm^{-1}: 1772
^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.37 (1H, dd, *J* = 18.0, 1.8 Hz), 2.62-2.67 (2H, m), 2.72 (1H, dd, *J* = 19.0, 9.6 Hz), 3.43-3.50 (1H, m), 5.08 (1H, ddd, *J* = 5.4, 5.4, 1.5 Hz), 5.53 (1H, ddd, *J* = 5.7, 4.2, 1.8 Hz), 5.74 (1H, ddd, *J* = 5.7, 4.5, 2.1 Hz)
^{13}C-NMR (75MHz, $CDCl_3$) δ: 33.03, 39.29, 45.36, 82.91, 129.62, 131.26, 176.78
MS m/z: 124 (M +)
Exact mass calcd. for $C_7H_8O_2$ (M +): 124.0524 Found: 124.0486.

INDUSTRIAL APPLICABILITY

[0044] The optically pure cis-4-cumyloxy-2-cyclopenten-1-ol and the analogues thereof provided by the present invention are useful intermediates for the synthesis of biologically and/or physiologically active compounds, and especially they are advantageously used as a starting material for the synthesis of prostaglandins. The present invention can also provide a shortened and simplified process for preparing an (-)-oxabicylco[3.3.0]oct-6-en-3-one which is useful as an intermediate for prostaglandins in higher yield in comparison with the prior art methods starting from a racemic compound or a cis/trans mixture. Accordingly, the present invention can provide a novel process for preparing the optically active lactone.

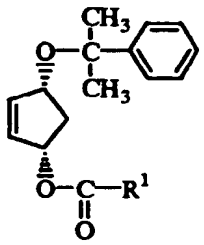
Claims

1. An optically active compound of formula (1).



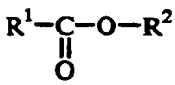
(1)

2. An optically active compound of formula (2)



(2)

wherein R^1 is a hydrogen atom or a straight or branched C_1-C_{10} alkyl group, optionally any hydrogen atom in the



(5)

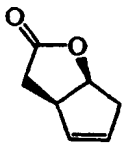
wherein R^1 is as defined above and R^2 is a hydrogen, a straight or branched C_1-C_{10} alkyl group or a straight or branched C_2-C_{10} alkenyl group, optionally any hydrogen atom in the alkyl or alkenyl group being substituted by a halogen atom.

7. The process of claim 6, wherein the hydrolase is a lipase.

8. The process of claim 6 or 7, wherein R^1 is the C_1-C_6 alkyl and R^2 is the C_2-C_6 alkenyl.

9. The process of claim 8, wherein R^1 is methyl and R^2 is vinyl.

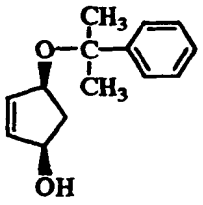
10. A process for preparing an (-)-oxabicylco[3.3.0]-oct-6-en-3-one represented by formula (6)



(6)

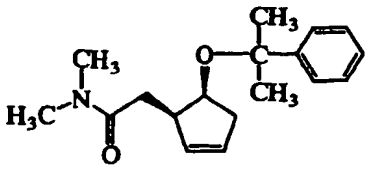
which comprises the steps of;

(a1) heating a compound of formula (1)



(1)

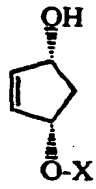
in the presence of dimethylacetamide dimethyl acetal to form a compound of formula (a-1)



(a-1)

and
(a2) treating the compound (a-1) with an acid in a solvent to form the compound (6).

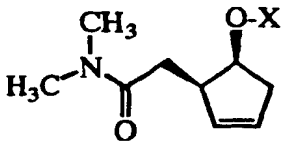
11. A process for preparing an (-)-oxabicylco [3.3.0]-oct-6-en-3-one of formula (6)



(b-3)

wherein X is as defined above,

(b4) heating the compound (b-3) in the presence of dimethylacetamide dimethyl acetal to form a compound of formula (b-4)



(b-4)

wherein X is as defined above, and

(b5) treating the compound (b-4) with an acid in a solvent to form the compound (6). 12. The process of claim 11, wherein X is t-butyldimethylsilyl group.

DOCID: <EP___1086942A1_I_>

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 11 9371

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
P,X	NAKASHIMA, H. ET AL.: "Chiral Preparation of Polyoxygenated Cyclopentanoids" SYNTHESIS, no. 6, 2000, pages 817-823, XP000941517 * the whole document *	1-12	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	6 December 2000	Janus, S

CATEGORY OF CITED DOCUMENTS

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